REMARKS

Claims 26-45 have been canceled without prejudice or disclaimer. Claims 46-57 have been added and therefore are pending in the present application. Claims 46-57 are supported throughout the specification, including the original claims. For example, the % identities recited in claims 46-51 are supported by page 7, line 33 – page 8, line 9 of the specification.

It is respectfully submitted that the present amendment presents no new issues or new matter and places this case in condition for allowance. Reconsideration of the application in view of the above amendments and the following remarks is requested.

I. The Objection to Claim 32

The Office objected to claim 32 as being a substantial duplicate of claim 31. This respectfully traversed.

Claims 31 and 32 use different transition terms – "comprises" vs. "consists of." The use of the different transition terms results in the claims having a different scope.

For the foregoing reasons, Applicants submit that the claims overcome this objection. Applicants respectfully request reconsideration and withdrawal of the objection.

II. The Rejection of Claims 26-29 under 35 U.S.C. 112

Claims 26-29 are rejected under 35 U.S.C. 112 as failing to comply with the written description requirement. This rejection is respectfully traversed.

It is well settled that a specification complies with the written description requirement if it provides "a precise definition, such as by structure, formula, chemical name, or physical properties of the claimed subject matter sufficient to distinguish it from other materials." See, e.g., *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398, 1404 (Fed. Cir. 1997); *Enzo Biochem v. Gen-Probe Inc.*, 63 U.S.P.Q.2d 1609, 1613 (Fed. Cir. 2002).

Applicants submit that the specification provides an adequate written description of the claimed invention. The claimed invention is directed to polypeptides having lysozyme activity and belonging to the GH25 family which (a) comprises an amino acid sequence having at least 90% identity with the sequence of amino acids 1 to 233 of SEQ ID NO: 2 or (b) is a fragment of the sequence of amino acids 1 to 233 of SEQ ID NO: 2 that has lysozyme activity. Thus, the claimed polypeptides are structurally similar. It would be routine for persons of ordinary skill in the art to identify each amino acid sequence which falls within the 90% sequence identity recitation. The

specification discloses a computer program for determining percent identity at page 3, line 31 – page 4, line 8.

The Office allegation without any scientific evidence that "one of ordinary skill would not be able to identify without further testing which of these proteins having at least 80-95% identity to SEQ ID NO: 2 (if any) [would] have lysozyme activity." This is respectfully traversed.

It is also well established in the art that there is a definitive relationship between protein function and % identity at the amino acid level. Percent identity is highly predictive of protein function. In particular, proteins that share 90% amino acid identity are known to possess the same catalytic/biochemical function. In fact, 90% identity is an extremely conservative criterion for judging functional similarity. A long history of structure-function studies has demonstrated that single domain proteins that share substantial similarity (and >30% identity) over their entire length (>80 residues) without introduction of numerous gaps are almost certainly homologous (derive from a common evolutionary ancestor) and share the same three-dimensional structure (see Marti-Renom et al., 2000, *Annu. Rev. Biophys. Biomol. Struct.* 29:291–325 (a copy of which is attached hereto)). At the 80-90% level of amino acid identity, orthologous enzymes in related species are virtually guaranteed to share the same catalytic function and substrate specificity. A simple search of any public database using the criteria above for a reference protein of interest will prove that there is a definitive relationship between protein function and % identity at the amino acid level.

Moreover, Guo et al., 2004, *Proc. Nat. Acad Sci USA* 101: 9205-9210 (a copy of which is attached hereto), observed that various residues of a protein are differentially sensitive to substitutions, and that tolerance of the entire protein to random change can be characterized by a probabilistic relationship termed the "x-factor." The x-factor is broadly defined as the probability that a random amino acid replacement will lead to functional inactivation. Moreover, they determined the x-factor to be 34% +/- 6%. Contrary to the Office's contention that random (even conservative) changes in a protein in the absence of structural information would adversely affect activity, the findings of Guo et al. support the contrary, *i.e.*, that proteins are generally tolerant to random amino acid substitutions, and the probability of destroying protein function is small.

Makiewicz et al., 1994, *J. Mol. Biol.* 240: 421-433 (a copy of which is attached hereto), examined 12 or 13 different amino acid substitutions at each residue across 90% of the 360 amino acid *E. coli lac* repressor protein. Reanalysis of their data by Guo et al. (2004) revealed an x-factor value of 34% which is identical to the value for random inactivation of human 3-methyladenine DNA glycosylase studied by Guo et al. Axe et al., 1998, *Biochem.* 37: 7157-7166 (a copy of which is

attached hereto), found that 95% of randomly introduced single amino acid substitutions did not lead to inactivated ribonuclease enzyme. Rennell et al., 1991, *J. Mol. Biol.* 222: 67-88 (a copy of which is attached hereto), found that approximately 84% of amino acid substitutions in T4 lysozyme did not cause inactivation.

Moreover, the specification describes methods for determining amino acids which are essential to the activity of a polypeptide. *See*, *e.g.*, page 15, lines 17-29. These methods are routine for persons skilled in the art.

Also, the specification discloses several assays for determining lysozyme activity at page 11, line 27 – page 12, line 5. *See also* Example 4. It would be routine for persons of ordinary skill in the art to determine if a polypeptide has lysozyme activity.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

III. The Rejection of Claims 26-29 under 35 U.S.C. 112

Claims 26-29 are rejected under 35 U.S.C. 112 "because the specification … does not reasonably provide enablement for any polypeptide having 80-95% identity to SEQ ID NO: 2 and having lysozyme activity." This rejection is respectfully traversed.

It is well settled that "[t]he first paragraph of section 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance." *In re Marzocchi*, 169 U.S.P.Q. 367, 369 (C.C.P.A. 1971). Moreover, "a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of section 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 U.S.P.Q. at 369.

"The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art ... The test is not quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed ..." *Ex parte Jackson*, 217 U.S.P.Q. 804 (Bd. Pat. App. 1982).

It is also well settled that an assertion by the Patent Office that the enabling disclosure is not commensurate in scope with the protection sought must be supported by evidence or reasoning substantiating the doubts so expressed. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (C.C.P.A. 1974). See also *U.S. v. Telectronics*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Bowen*, 181 U.S.P.Q. 48 (C.C.P.A. 1974); *Ex parte Hitzeman*, 9 U.S.P.Q.2d 1821 (BPAI 1988).

Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988).

Applicants submit that the specification enables the claimed invention. The claimed invention is directed to polypeptides having lysozyme activity and belonging to the GH25 family which (a) comprises an amino acid sequence having at least 90% identity with the sequence of amino acids 1 to 233 of SEQ ID NO: 2 or (b) is a fragment of the sequence of amino acids 1 to 233 of SEQ ID NO: 2 that has lysozyme activity. It would be routine for persons of ordinary skill in the art to identify each amino acid sequence which falls within the 90% sequence identity recitation. The specification discloses a computer program for determining percent identity at page 3, line 31 – page 4, line 8.

Moreover, the specification contains an extensive disclosure of how to produce the polypeptides. For example, the specification discloses that genes encoding the polypeptides may be cloned using, *e.g.*, SEQ ID NO: 1 as a probe (*see*, *e.g.*, pages 9 and 10). The specification also discloses that the polypeptides can be produced by methods well known in the art such as mutagenesis, recombination and/or shuffling (*see* page 8, line 25 – page 9, line 13).

The specification also discloses several known assays for determining lysozyme activity at page 11, line 27 – page 12, line 5. *See also* Example 4. It would be routine for persons of ordinary skill in the art to determine if a polypeptide has lysozyme activity.

This evidence establishes that the specification enables the claimed invention. Application of the *Wands* factors to these facts further supports the conclusion that the claims are enabled. First, the present invention is in the field of molecular biology. The *Wands* court has already held that the level of skill in this art is high. *Wands*, 858 F.2d at 740. Second, the specification provides an extensive disclosure for producing the claimed polypeptides. Third, as

in *Wands*, the methods of making the claimed polypeptides and screening for lysozyme activity are known in the art and described in the specification. Fourth, given the extensive guidance given in the specification and the high level of skill in the art, the experimentation involved to produce other polypeptides within the scope of the claims is routine and well known to those of ordinary skill in the art. As held by the *Wands* court, "The test is not merely quantitative since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experiment should proceed." *Id.* at 737.

As of Applicants' effective filing date, persons of ordinary skill in the art were able to routinely produce thousands of variants of SEQ ID NO: 2 through mutagenesis and other techniques in a short period of time. Furthermore, at page 15, lines 17-29, the specification discloses how one of ordinary skill in the art could identify essential amino acids and the active site in the sequence of SEQ ID NO: 2. Thus, one of ordinary skill in the art can predict which modifications, if any, would result in a loss of the desired activity/utility.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

IV. The Deposit Requirement

Claims 26-33 are rejected under 35 U.S.C. 112 as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Office requested that Applicants provide the assurances required under 35 C.F.R. 1.801 – 1.809 for the strain DSM 16084.

As requested by the Examiner, Applicants confirm that biological material was deposited at Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH (DSM) under the Budapest Treaty and assigned accession number DSM 16084. All restrictions on the availability to the public of said deposited material will be irrevocably removed upon the granting of the U.S. patent. Said deposit will be maintained for (a) thirty years, (b) at least five years after the most recent request for the furnishing of a sample of the deposit is received by the depository, or (c) the enforceable life of the U.S. patent granted from this application, whichever is longest. If the deposited material becomes inviable during the above term, the deposited material will be replaced.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 112. Applicants respectfully request reconsideration and withdrawal of the rejection.

V. The Rejection of Claims 26-33 under 35 U.S.C. 101

Claims 26-33 are rejected under 35 U.S.C. 101 because the claimed invention is directed toward non-statutory subject matter. Claims 26-33 have been rewritten as claims 46-54 to address this rejection. Applicants therefore submit that this rejection has been overcome.

VI. The Rejection of Claim 26 under 35 U.S.C. 102

Claim 26 is rejected under 35 U.S.C. 102(b) as anticipated by Felch et al. (250(10): 3713-3720 (1975)). This rejection is respectfully traversed.

Felch et al. disclose the amino acid sequence of a lysozyme from a *Chalaropsis* species.

However, Felch et al. do not disclose a lysozyme of the present invention. In particular, Felch et al. do not disclose a fragment of the sequence of amino acids 1 to 233 of SEQ ID NO: 2 which has lysozyme activity.

The Office states that the lysozyme disclosed in Felch et al. has "several fragments of varying lengths that match different portions fragments of SEQ ID NO: 2…." This is respectfully traversed.

Fragments are defined in the present application as "a polypeptide retaining the lysozyme activity but having one or more amino acids deleted from the amino acid/or carboxyl terminus" (page 4, lines 10-13). None of the fragments contained in the lysozyme disclosed in Felch et al. has lysozyme activity.

For the foregoing reasons, Applicants submit that the claims overcome this rejection under 35 U.S.C. 102. Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. Conclusion

In view of the above, it is respectfully submitted that all claims are in condition for allowance. Early action to that end is respectfully requested. The Examiner is hereby invited to contact the undersigned by telephone if there are any questions concerning this amendment or application.

Respectfully submitted,

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